

(19) World Intellectual Property  
Organization  
International Bureau



13 MAY 2005

(43) International Publication Date  
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number  
**WO 2004/045511 A3**

(51) International Patent Classification<sup>7</sup>: **C07D 311/04**,  
A61K 31/35, 31/215

(US). NICOLAOU, Kyriacos, C. [US/US]; 9625 Black-  
gold Road, La Jolla, CA 92037 (US). ROECKER, An-  
thony, J. [US/US]; 3337 Clairemont Drive, #4, San Diego,  
CA 92117 (US).

(21) International Application Number:  
PCT/US2003/036123

(74) Agents: REITER, Stephen, E. et al.; Foley & Lardner,  
P.O. Box 80278, San Diego, CA 92138-0278 (US).

(22) International Filing Date:  
14 November 2003 (14.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/426,664 15 November 2002 (15.11.2002) US  
10/658,115 8 September 2003 (08.09.2003) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,  
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,  
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,  
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,  
SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,  
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(63) Related by continuation (CON) or continuation-in-part  
(CIP) to earlier applications:

US	60/426,664 (CIP)
Filed on	15 November 2002 (15.11.2002)
US	10/658,115 (CIP)
Filed on	8 September 2003 (08.09.2003)

(84) Designated States (*regional*): ARIPO patent (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,  
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*): THE  
SALK INSTITUTE FOR BIOLOGICAL STUDIES  
[US/US]; 10010 North Torrey Pines Road, La Jolla, CA  
92037 (US). THE SCRIPPS RESEARCH INSTITUTE  
[US/US]; 10550 North Torrey Pines Road, La Jolla, CA  
92037 (US).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): DOWNES, Michael,  
R. [AU/US]; 3440 Lebon Drive, Apt. 4210, San Diego, CA  
92122 (US). EVANS, Ronald, Mark [US/US]; 1471 Cot-  
tontail Lane, La Jolla, CA 92037 (US). HUGHES, Robert  
[GB/US]; 800 N. Lindberg, Q403, Creve Couer, MO 63167

(88) Date of publication of the international search report:  
8 July 2004

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: NON-STEROIDAL FARNESOID X RECEPTOR MODULATORS

(57) Abstract: The efficient regulation of cholesterol synthesis, metabolism, acquisition, and transport is an essential component of lipid homeostasis. The farnesoid X receptor (FXR) is a transcriptional sensor for bile acids, the primary product of cholesterol metabolism. Accordingly, the development of potent, selective, small molecule agonists, partial agonists, and antagonists of FXR would be an important step in further deconvoluting FXR physiology. In accordance with the present invention, the identification of novel potent FXR activators is described. Two derivatives of invention compounds, bearing stilbene or biaryl moieties, contain members that are the most potent FXR agonists reported to date in cell-based assays. These compounds are useful as chemical tools to further define the physiological role of FXR as well as therapeutic leads for the treatment of diseases linked to cholesterol, bile acids and their metabolism and homeostasis.

WO 2004/045511 A3

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/36123

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07D 311/04; A61K 31/35; 31/215

US CL : 549/385, 399, 400, 401, 404, 408, 514; 560/45, 48; 564/123, 190; 514/454, 456, 457, 534

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/385, 399, 400, 401, 404, 408, 514; 560/45, 48; 564/123, 190; 514/454, 456, 457, 534

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE -Structure search**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,151,442 A (GARCIA et al) 29 September 1992 (20.09.1992)	1-32

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;"

document member of the same patent family

Date of the actual completion of the international search

05 March 2004 (05.03.2004)

Date of mailing of the international search report

18 MAY 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Bernard Dentz

Telephone No. 703 308-1235